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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,793	03/22/2004	Teit E. Johansen	19313-001CON	2372

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EXAMINER

WANG, CHANG YU

ART UNIT	PAPER NUMBER
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1649

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06/01/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/806,793	Applicant(s) JOHANSEN ET AL.	
	Examiner Chang-Yu Wang	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 80-83 and 87-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 80-83 and 87-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/18/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/9/09 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 3/9/09 is acknowledged. Claims 1-79 and 84-86 are cancelled. Claim 80 is amended. Claims 80-83 and 87-93 are pending in this application and under examination in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on 3/9/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

5. The rejection of claims 80-83 under 35 U.S.C. 112, first paragraph, because the specification does not enable the claimed invention commensurate in scope with the claims is withdrawn in response to Applicant's amendment to the claims.

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The rejection of claims 80-83 and 87-93 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendment to the claims.

Claim Rejections/Objections Maintained

In view of the amendment filed on 3/9/09, the following rejections are maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 80-83, 87-90 and 93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan) in view of US 6,284,540 (Milbrandt et al). The rejection is maintained for the reasons made of record.

On p. 4-6 of the response, Applicant argues that Milbrandt does not teach that neublastin/artemin (NBN/ARTN) can bind and activate GFR α 1 or in vivo activation of

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GFR α 1 by NBN/ARTN because Milbrandt only reports the activation of GFR α 1 in neuroblastoma cells overexpressed with GFR α 1 in vitro, which is an artifact of the experiments. Applicant argues that GDNF is the exclusive physiological ligand for GFR α 1 because neublastin/artemin (NBN/ARTN) is structurally and functionally distinct from GDNF. Applicant further cites Rakowiez (J. Neurosci. 2002. 22: 3953-62), and Carmillo (Biochemistry. 2005. 44: 2545-54) and Teit Johansen's declaration in support of the arguments. Applicant arguments have been fully considered but they are not persuasive.

In response, regardless of what real mechanisms in treating retinal ganglion cell degeneration or macular degeneration by NBN/ARTN are, Milbrandt (US 6,284,540) teaches that NBN/ARTN is a member of the GDNF family and have similar neurotrophic activity as GDNF. In addition, Milbradt teaches that NBN/ARTN can bind and activate GFR α 1 (figure 11; examples 7-8). The binding of NBN/ARTN to GFR α 1 is also supported by Carmillo (see abstract) regardless of whether Carmillo was able to reproduce the data of activation of GFR α 1 by ARTN.

In this case, it is obvious to use another growth factor in the GDNF family with an expectation of success to treat retinal or macular degeneration based on the combined teachings of Yan (US5641749) and Milbrandt (US6284540) at the time of the instant invention. Yan (US 5,641,749) has taught a method of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning columns 4-5, and column 19, lines 28-30). Milbrandt teaches that NBN/ARTN is a member of the

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GDNF family, which functions similarly to other members of the family, and has been shown to be able to bind and activate GFR α 1 (i.e. the receptor for GDNF). Thus, it would have been obvious to use NBN/ARTN or cells expressing NBN/ARTN as disclosed by Milbrandt to replace GDNF in the Yan's method because successful and similar results of substituting GDNF with NBN/ARTN are expected in the treatment of glaucoma or retinal degeneration.

Note that it is obvious to combine prior art elements according to known methods to yield predictable results and it is also obvious as to simply substitute one known element for another to obtain predictable results.

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

On p.6 of the response, Applicant argues that there is no motivation or suggestion to combine the applied references to achieve the claimed method because Milbrandt does not teach a method of using Neublastin/artemin in treatment of macular degeneration, glaucoma or retinitis pigmentosa and Yan only teaches use of GDNF in treatment of retinal ganglion cell degeneration. Applicant also cites *DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Col, SIBA Neuroscience, Inc. v. Cadus Pharma. Corp., In re Fulton* and *KSR* in support of the arguments. Applicant arguments have been fully considered but they are not persuasive.

In response, as previously made of record, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument with regard to no motivation to combine, it is noted that "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

In addition, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07.

In this case, Yan discloses methods of treating retinal ganglion cell degeneration caused by glaucoma by the intraocular implantation of glial cell line-derived neurotrophic factor (GDNF)-expressing cells (see paragraph spanning col. 4-5, and column 19, lines 28-30). Although Yan does not teach the use of NBN/ARTN, Milbrandt teaches that NBN/ARTN is a member of the GDNF neurotrophic factor family and is useful for treating conditions involving neuronal degeneration including degeneration of retina (i.e. a type of neuron). Since NBN/ARTN is a member of the GDNF family and can bind and activate GFR α 1 (i.e. the receptor for GDNF), it would have been expected that NBN/ARTN would act and function similarly as GDNF and would be effective in

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treatment of retinal degeneration as GDNF as disclosed by Yan. Accordingly, the rejection is maintained.

7. Claims 80-83 and 87-93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,749 (Yan) in view of US 6,284,540 (Milbrandt) as applied to claims 80-83, 87-90 and 93 above, and further in view of US 6299895 (Hammang). The rejection is maintained for the reasons made of record.

On p. 7-8 of the response, Applicant argues that the combined references would not achieve the claimed invention. Applicant argues that although Milbrandt teaches NBN/ARTN binds and activates $GFR\alpha 1$, Milbrandt's teaching is incorrect based on Rakowicz and Carmillo's teachings as shown in Teil Johansen's declaration. Applicant further argues that and Hammang does not cure the deficiency of Milbrandt because Hammang does not teach the use of NBN/ARTN in the treatment of macular degeneration or retinitis pigmentosa. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, as previously made of record and as set forth above, Yan teaches a method of treating retinal ganglion cell degeneration caused by glaucoma with GDNF. In addition, Hammang (US6299895) teaches the use of GDNF in treatment of macular degeneration and retinitis pigmentosa as recited in instant claims 80, 91 and 92 (see col.5, lines38-64; col. 10, line 16-col.11, line 67; examples 1-5). Although Yan and Hammang do not teach use of NBN/ARTN, Milbrandt teaches that NBN/ARTN is a member of the GDNF family and can bind and activate $GFR\alpha 1$. Thus, similar and

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successful results of substitution of GDNF with NBN/ARTN in the methods of Yan and Hammang would have been expected because NBN/ARTN is a member of the GDNF family and can act as GDNF by binding and activating GFR α 1 based on Milbrandt's teaching.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87-93 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating photoreceptor loss in the retina of patients afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of said patient a cell line expressing a Neublastin polypeptide comprises one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 9-12, does not reasonably provide enablement for a method of treating the above eye disorders comprising administering a cell line expressing a Neublastin polypeptide, which comprises an amino acid sequence that is at least 95% homologous to the amino acid sequence of SEQ ID NO: 12 or comprising any amino acid sequences of SEQ ID NOs 9-12 (i.e. including undefined fragments) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

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commensurate in scope with these claims. The rejection is reinstated and maintained for the reasons below.

On p. 8 of the response, Applicant argues that the rejection has been overcome because independent claim 80 has been amended to recite an amino acid sequence that is at least 95% identical to the full length of amino acid sequence of SEQ ID NO:12. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, based on the specification (p. 2 of the instant specification), dependent claims 87-90 also encompass fragments, variants and derivatives of wild type Neublastin, SEQ ID NO:12 because claims 87-90 recite "an amino acid sequence of SEQ ID NOs:9-12", which encompasses different fragments with different sizes of amino acid sequences derived from the amino acid sequence of SEQ ID NOs:9-12. As previously made of record, the instant specification provides insufficient guidance as to how to make and use these structurally undefined variants and derivatives and also fails to teach how to use these structurally and functionally undefined fragments or variants of SEQ ID NO:12 in the method of treating macular degeneration or retinitis pigmentosa.

The instant specification fails to provide sufficient guidance as to what other structures/amino acid sequences can or cannot be included/changed in all Neublastin polypeptides including fragments, variants and derivatives in order to preserve the activity of SEQ ID NO:12 and thus to be used in treating macular degeneration, retinitis pigmentosa or glaucoma. Thus, it is unpredictable whether all of the claimed Neublastin

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polypeptides including variants, derivatives and fragments can maintain their activity as that of SEQ ID NO:12.

Accordingly, a skilled artisan would not know how to make and use all of the Neublabin polypeptides including fragments, variants and derivatives in the claimed method, indicating that undue experimentation is required to practice the claimed invention. Note that the scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03.

Claim Rejections - 35 USC § 112

9. Claims 87-93 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

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had possession of the claimed invention. The rejection is maintained for the reasons made of record.

On p. 8 of the response, Applicant argues that the rejection has been overcome because independent claim 80 has been amended to recite an amino acid sequence that is at least 95% identical to the full length of amino acid sequence of SEQ ID NO:12. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the claimed NBN polypeptides used in the claimed method of claims 88-93 are not limited to the amino acid sequence of SEQ ID NO:12 or the amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:12 because the claimed polypeptides used in the claimed method encompass structurally undefined fragments, derivatives and variants derived from the amino acid sequence of SEQ ID NO:12.

The specification fails to teach what other sequences or defined structures are required for the claimed polypeptides including fragments, derivatives and variants in order to preserve the neurotrophic activity of SEQ ID NO:12; and thereby to be used in the claimed method. Thus, the specification fails to reasonably demonstrate Applicant's possession of such broad genus of NBN polypeptides and thus Applicant is not in possession of the claimed method of using a broad genus of NBN polypeptide. Accordingly, the rejection of the claimed method for failing to meet the written description requirement is maintained.

Conclusion

10. NO CLAIM IS ALLOWED.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
April 24, 2009

/Christine J Saoud/
Primary Examiner, Art Unit 1647